REMARKS

I. Status of the Claims

The claims have been amended herein to recite the full term "lipoic acid" in place of the abbreviated "LA" for added clarity. Claims 5-15 have been withdrawn under 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Applicants reserve the right to prosecute non-elected subject matter in one or more continuing application(s). Claims 1-4 are therefore pending and are presented for reconsideration.

II. Discussion of Rejections Under 35 U.S.C. § 103

A. Rejection of Claims 1-4 Over Kulkarni *et al.* in view of Packer *et al.*

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kulkarni *et al.* (U.S. Patent 6,365,407, filed March 2001) in view of Packer *et al.*, ("Alpha-Lipoic Acid as a Biological Antioxidant"; 1995, *Free Rad. Biol. And Med.* 19:227-250). According to the Action, while Kulkarni *et al.* do not disclose lipoic acid, it discloses a method comprising culturing a Taxus cell on a medium comprising 1-5 mg/L of antioxidants (claim 5), and Packer *et al.* teach lipoic acid is a biological antioxidant. Further according to the Action, at the time the invention was made, when culturing a plant cell on a medium comprising an antioxidant as taught by Kulkarni *et al.*, it would have been obvious to one skilled in the art to use lipoic acid as the particular antioxidant, because Packer *et al.* teach that lipoic acid is the "ideal," "universal antioxidant" (p28, right column, paragraph 2). Applicants traverse for at least the reasons discussed below.

Applicants initially note that the cited references fail to teach or suggest the claimed method of culturing a plant cell on a media comprising 5uM to 100uM lipoic acid. While Packer *et al.* allegedly teach lipoic acid as a biological antioxidant, ***Packer et al. do not teach the use of lipoic acid as an appropriate antioxidant with regard to plant cells***. The Packer reference concerns only mammalian species, tissues, and cells, e.g. "animals" (page 227); "humans" (*Id.*); "patients" (page 243); "mice" (page 236); "guinea pigs" (page 229); "rats" (*Id.*); "liver" (page 237); "skin" (*Id.*); "brain" (*Id.*); "human fibroblasts" (*Id.*); "mammalian cells" (page 237); and "Jurkat T-cells" (page 235). Mammalian cells are very different than plant cells, lacking a number of common plant intracellular components including chloroplasts, vacuoles, and chlorophyll. Culturing of plant and animals cells is also vastly different, given the enormous

physiological differences between the cells. As such, the Packer reference provides no guidance as to how lipoic acid might interact with these, or any other plant cell components. In contrast, the pending claims are directed toward a method for transforming a plant cell using media comprising lipoic acid. Any suggestion that lipoic acid is an "ideal" or "universal antioxidant" such as by Packer *et al.* in the context of animal cells would therefore have no bearing on the current claims.

Kulkarni *et al.* relates to use of "a number of antioxidants together with picloram" in order to promote taxane production by cells of the Himalayan Yew. Though the reference lists activated charcoal, ascorbic acid, and PVP, this combination of antioxidants does not include lipoic acid, as lipoic acid is not disclosed anywhere in the Kulkarni *et al.* patent. Furthermore, the Kulkarni patent fails to teach or even suggest the use of antioxidants in connection with genetic transformation. As such, the Kulkarni patent does not teach the method of the claimed invention, and would not provide a reasonable expectation of success with respect to the claimed invention.

Even more significantly, it must be noted that the current invention yields surprising and unexpected results affirmatively demonstrating the non-obviousness of the claimed invention. The Court in *KSR* stated that "[T]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 82 USPQ 2d 1387, 1395 (2007). In the present case, the results obtained by the invention are anything but predictable. While Packer *et al.* is asserted to teach that lipoic acid is an effective antioxidant for use in mammalian systems and Kulkarni *et al.* is asserted to teach that a combination of antioxidants in further combination with picloram aids taxane production in undifferentiated cells of Himalayan Yew, the current working examples in the specification demonstrate significantly different and surprising results that could in no way be predicted by the art.

For instance, the working examples demonstrate both an increase in transient expression of a heterologously introduced marker gene when using lipoic acid, as well as an increase in the percentage of transgenic plants produced per explant by 2.7 to 4.3 fold. The impact of lipoic acid on the percentage of transgenic plants produced per explant is shown in Table 3. Treatment with 10uM lipoic acid increased the percentage of transgenic plants produced per explant from 40.1% to 178.7%. Similarly, LA's impact on expression of the marker gene beta-glucuronidase (GUS) is shown in Table 2. Treatments of lipoic acid at concentrations of 10 and 50uM

increased the percentage of explants having high transient expression from 10% to 60.9%. *See* Table 2.

LA's affect on browning of tissue was also assessed using a cultivar of tomato species, *Lycopersocon esculentum.* Tissue browning was measured in and around the poked region on cotyledon explants. All treatments of lipoic acid at concentrations of 5, 10 50, and 100uM had 1.5 to 1.8 fold increase in the number of explants scored as low tissue-browning severity, respectively, compared to the treatment without lipoic acid. *See* Table 1.

The foregoing results represent a significant advance that could in no way have been predicted based on the knowledge in the art. This evidence establishes the non-obviousness of the claimed invention. Withdrawal of the rejection is thus respectfully requested.

B. Rejection of Claims 1-4 Over Benson *et al.* in view of Packer *et al.*

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Benson *et al.* (1997, *Phyton* 37(3):31-38) in view of Packer *et al.* ("Alpha-Lipoic Acid as a Biological Antioxidant"; 1995, *Free Rad. Biol. And Med.* 19:227-250). According to the Action, Benson *et al.* disclose a method comprising culturing a plant cell on a media, and that plant cell culture is affected by free radicals, while Packer *et al.* teach lipoic acid is a biological antioxidant. It is further asserted that it would have been obvious to one ordinary skill in the art to modify the method taught by Benson *et al.* to use lipoic acid as described by Packer *et al.* as an antioxidant. Applicant respectfully traverses the rejection as set forth below.

Applicants initially note that, as explained above, Packer *et al.* does not teach the use of lipoic acid as an appropriate antioxidant with regard to plant cells. Also, while Benson *et al.* is cited as teaching that plant cell culture is affected by free radicals, the reference itself states that:

> [W]e strongly caution the use of tissue cultures as 'models' for the study of stress responses without prior knowledge of the culture's developmental history. Habituation, culture age and competence greatly influence the oxidative status off cultures and may confound experimental interpretations. Benson *et al. at* 37.

The Benson reference further states that "at present there exists no direct evidence to implicate free radicals, activated oxygen species and/or their reaction products as causal agents in either genetic or epigenetic instability in plant cultures." Benson *et al. at* 35. The authors also warn that oxidative processes may have a direct role in *in vitro* development, and caution against solely considering the negative aspects of free radicals. A person of skill in the art would not interpret the reference to teach the use of antioxidants in tissue culture, because the authors

themselves suggest there is too little understanding of antioxidants to make it a worthwhile pursuit. Without the motivation to use an antioxidant in tissue culture, there is no motivation to find an appropriate antioxidant.

Applicants further note that, as explained above, the current invention provides surprising and unexpected results that demonstrate the non-obviousness of the invention. Again, the Court in *KSR* stated "[T]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 82 USPQ 2d 1387, 1395 (2007). However, in the present case the yielded results are anything but predictable. As noted above, both an increase in transient expression of a heterologously introduced marker gene was observed when using lipoic acid, as well as an increase in the percentage of transgenic plants produced per explant by 2.7 to 4.3 fold. The impact of lipoic acid on the percentage of transgenic plants produced per explant is shown in Table 3. Treatment with 10uM lipoic acid increased the percentage of transgenic plants produced per explant from 40.1% to 178.7%. Similarly, LA's impact on expression of the marker gene beta-glucuronidase (GUS) is shown in Table 2. Treatments of lipoic acid at concentrations of 10 and 50uM increased the percentage of explants having high transient expression from 10% to 60.9%. *See* Table 2. A significant decrease in "browning" was also observed during tissue culture.

The foregoing results could in no way be predicted in the art. Packer *et al.* simply relates to lipoic acid in relation to various mammalian systems. Benson *et al.* is simply asserted to teach that tissue culture is affected by free radicals, and the reference even concedes that the authors "strongly caution the use of tissue cultures as 'models' for the study of stress responses without prior knowledge of the culture's developmental history." One of skill in the art would thus not interpret these references as predicting the positive effect on plant cell transformation and gene expression that is achieved when using a media comprised of lipoic acid. Thus, the results disclosed in the present application are surprising, and therefore demonstrate the non-obviousness of the claims.

The theory set forth in the Action that one might have been motivated to try to do what the present invention in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. A general motivation to create some unspecified protocol does not make obvious a specifically-defined method. More is needed and it is not found here. A general incentive does not make obvious a particular unexpected result,

nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

Thus, as alleged by the Action, the cited references teach a method comprising culturing a plant cell on a media, and that plant cell culture is affected by free radicals, and that lipoic acid is a biological antioxidant. However, the authors of the Benson reference themselves caution against the use of tissue cultures as "models," thus limiting the predictive value of the reference. The Packer reference concerns only mammalian species, tissues, and cells, and does not teach the use of lipoic acid as an appropriate antioxidant with regard to plant cells. In contrast, the results disclosed in the present application include reduction of "browning" during tissue culture, increase in transient expression of a marker gene, and an increase in the percentage of transgenic plants produced per explant by a 2.7 to 4.3 fold. The results disclosed in the present application are surprising, and therefore demonstrate non-obviousness. In view of the above, Applicants therefore respectfully request withdrawal of the obviousness rejection.

III. Conclusion

This is submitted to be a complete response to the referenced Office Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned at (214)259-0931 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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